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BUDAPEST

Translation from Hungarian

---------- THE REPUBLIC OF HUNGARY ----------

---------- **CERTIFICATE OF PRIORITY** ----------

Case No.: P0202213 ----------

The Hungarian Patent Office hereby certifies that Richter Gedeon Vegyészeti Gyár Rt. /Budapest/, filed a patent application in Hungary on 10th July, 2002, under registration No. 28857/02 for its invention entitled "Solid-supported parallel synthesis for the manufacture of new carboxylic acid amid derivatives". ----------

The copy attached is in full conformity with the Annex filed simultaneously with the Application. -

Given at Budapest, this 20th day of November, in the year 2003. ----------

Certified true copy ----------

illegible signature ----------

(SZABÓ Emília, Deputy Head of Patent Department) -

The Hungarian Patent Office certifies in this Priority certificate that the said applicant(s) filed a patent application at the specified date under the indicated title, application number and registration number. The attached photocopy is a true copy of specification filed with the application. ----------

L.S.: Hungarian Patent Office----------

7773h /1 2003 OFPI

Hitelesen bizonyítom, hogy ez a fordítás a fenti magyar
Idefűzött
szöveggel
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szövegnek ..... részévé
mindenben megegyezik.

Budapest, 19 2003. DEC. - 3

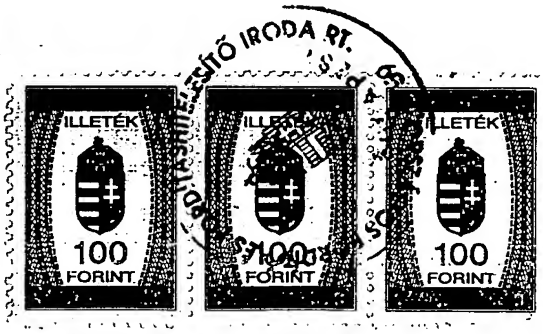
Az Országos Fordító és Fordításhitelesítő Iroda igazgatója

No. 7773h /19 2003

The Hungarian National Office for Translations and Attestations hereby officially certifies that the above translation is in full conformity with the (attached) original passage (s) marked in the (attached) original.

Budapest 03. 12. /19 2003

for the Director



MAGYAR KÖZTÁRSASÁG

ELSŐBBSÉGI TANÚSÍTVÁNY

Ügyszám: P0202213

A Magyar Szabadalmi Hivatal tanúsítja, hogy

Richter Gedeon Vegyészeti Gyár Rt., Budapest,

Magyarországon

2002. 07. 10. napján 28857/02 iktatószám alatt,

Szilárd-fázisú párhuzamos szintézis új karbonsavamidszármazékok előállítására

című találmányt jelentett be szabadalmazásra.

Az idefűzött másolat a bejelentéssel egyidejűleg benyújtott melléklettel mindenben megegyezik.

Budapest, 2003. év 11. hó 20. napján

Szabó Emilné

A kiadmány hiteléül: Szabó Emilné osztályvezető-helyettes

The Hungarian Patent Office certifies in this priority certificate that the said applicant(s) filed a patent application at the specified date under the indicated title, application number and registration number. The attached photocopy is a true copy of specification filed with the application.

P 02 02213

Solid-supported parallel synthesis of new carboxylic acid amide derivatives

Inventors:

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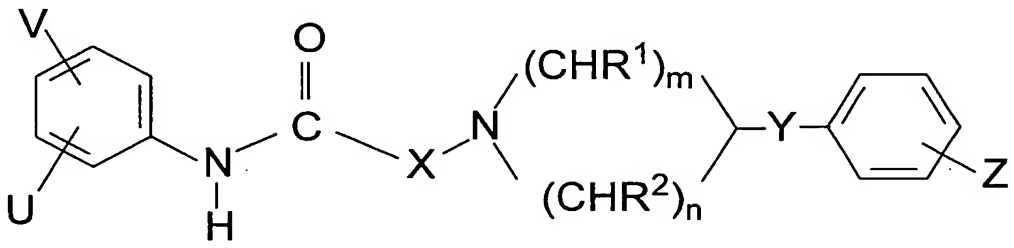
Applicant: Gedeon Richter Ltd, Budapest, Hungary

The invention relates to the fast, effective and automated preparation of new carboxylic acid amide derivatives of formula (I)



(I)

- wherein

V and U independently are hydrogen or halogen atom, hydroxyl, cyano, nitro, amino, C_1-C_4 alkylamino optionally substituted by a halogen atom or halogen atoms, arylamino optionally substituted by a halogen atom or halogen atoms, aralkylamino optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkylsulfonamido optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkanoylamido optionally substituted by a halogen atom or halogen atoms, arylsulfonamido, C_1-C_4 alkylsulfonyloxy, carboxyl, trifluoromethyl, trifluoromethoxy, C_1-C_4 alkyl-SO_2-NH-CH_2-, NH_2-$(CH_2)_{1-4}$-SO_2-NH-, NH_2-$(CH_2)_{1-4}$-(CO)-NH-, sulfamoyl [NH_2-SO_2-], formyl [-CHO], amino-methyl [-CH_2-NH_2], hydroxymethyl, C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, halogenomethyl, tetrazolyl group, or C_1-C_4 alkoxy, C_1-C_4

alkoxycarbonyl, C_1-C_6 alkanoyloxy, phenyl or C_1-C_4 alkoxy groups, optionally substituted by amino group, or

the neighbouring V and U groups in given case together with one or more identical or different additional hetero atom and -CH= and/or -CH_2- groups can form an optionally substituted 4-7 membered homo- or heterocyclic ring, preferably morpholine, pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

X stands for -CO- or -CH_2- group,

Y is oxygen atom, as well as C_1-C_4 alkylene, C_1-C_4 alkynylene, cycloalkylene, aminocarbonyl, -NH-, -N(alkyl)-, -CH_2O-, -CH(OH)-, -OCH_2- group, - wherein alkyl is a C_1-C_4 alkyl group -,

Z is hydrogen or halogen atom, nitro, amino, C_1-C_4 alkyl, C_1-C_4 alkoxy, cyano, trifluoromethyl, hydroxyl or carboxyl group,

R^1 and R^2 independently are hydrogen atom or alkyl group, or R^1 and R^2 together form an optionally substituted C_1-C_3 bridge and

n and m independently are 0-3, with the restriction, that n and m can not be 0 at the same time,

and optical antipodes or racemates and/or pharmaceutically acceptable salts thereof formed with acids and bases with the proviso that

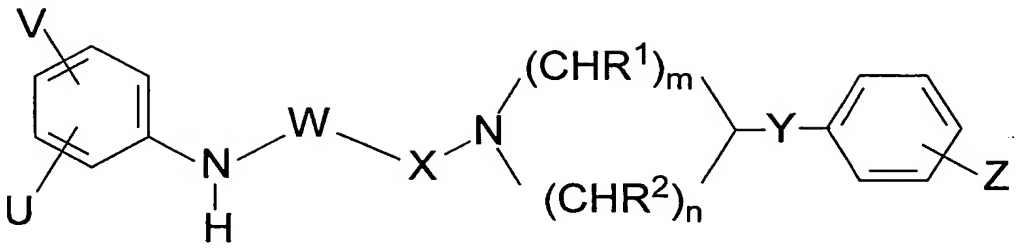
when Z means hydrogen atom, Y means -CH_2- group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, X means -CH_2- group and V means hydrogen atom, then the meaning of U is other than a 4-bromo substituent and

when Z means hydrogen atom, Y means -CH_2- group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, X means -CO- group and V means hydrogen atom, then the meaning of U is other than a 4-carboxyl or 4-etoxycarbonyl substituent,

which are antagonists of NMDA receptor or are intermediates for preparing thereof by liquid-phase parallel synthesis.

Background of the invention.

Gedeon Richter filed a patent application (P 01 03055) on the invention relates to new carboxylic acid amide derivatives of formula (IA)



(IA)

- wherein

V and U independently are hydrogen or halogen atom, hydroxyl, cyano, nitro, amino, C_1-C_4 alkylamino optionally substituted by a halogen atom or halogen atoms, arylamino optionally substituted by a halogen atom or halogen atoms, aralkylamino optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkylsulfonamido optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkanoylamido optionally substituted by a halogen atom or halogen atoms, arylsulfonamido, C_1-C_4 alkylsulfonyloxy, carboxyl, trifluoromethyl, trifluoromethoxy, C_1-C_4 alkyl-SO_2-NH-CH_2-, NH_2-$(CH_2)_{1-4}$-SO_2-NH-, NH_2-$(CH_2)_{1-4}$-(CO)-NH-, sulfamoyl [NH_2-SO_2-], formyl [-CHO], amino-methyl [-CH_2-NH_2], hydroxymethyl, C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, halogenomethyl, tetrazolyl group, or C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkanoyloxy, phenyl or C_1-C_4 alkoxy groups, optionally substituted by amino group, or

the neighboring V and U groups in given case together with one or more identical or different additional hetero atom and -CH= and/or -CH_2- groups can form an optionally substituted 4-7 membered homo- or heterocyclic ring, preferably morpholine, pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

W and X independently are carbonyl, methylene, -C(=NOH)-, -C(=NH)-, -CH(alkyl)- group - wherein alkyl is a C_1-C_4 alkyl group - with the restriction, that the meaning of W and X can not be methylene at the same time

Y is oxygen atom, as well as C_1-C_4 alkylene, C_1-C_4 alkynylene, cycloalkylene, aminocarbonyl, -NH-, -N(alkyl)-, -CH_2O-, -CH(OH)-, -OCH_2- group, - wherein alkyl is a C_1-C_4 alkyl group -,

Z is hydrogen or halogen atom, nitro, amino, C_1-C_4 alkyl, C_1-C_4 alkoxy, cyano, trifluoromethyl, hydroxyl or carboxyl group,

R^1 and R^2 independently are hydrogen atom or alkyl group, or R^1 and R^2 together form an optionally substituted C_1-C_3 bridge and

n and m independently are 0-3, with the restriction, that n and m can not be 0 at the same time,

and optical antipodes or racemates and/or pharmaceutically acceptable salts thereof formed with acids and bases - with the proviso that

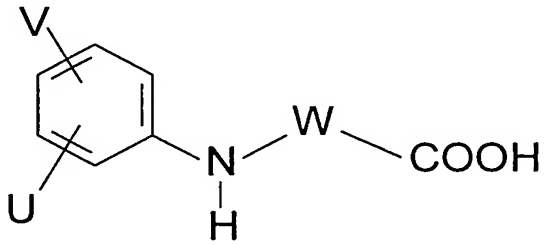
when Z means hydrogen atom, Y means -CH_2- group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, W means -CO- group, X means -CH_2- group and V means hydrogen atom, then the meaning of U is other than a 4-bromo substituent and

when Z means hydrogen atom, Y means -CH_2- group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, both of W and X mean -CO- group and V means hydrogen atom, then the meaning of U is other than a 4-carboxyl or 4-etoxycarbonyl substituent,

which are antagonists of NMDA receptor or are intermediates for preparing thereof.

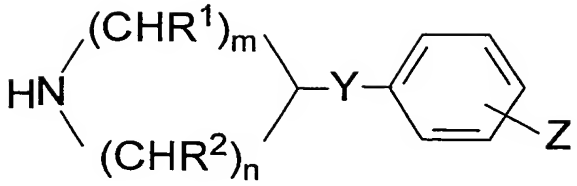
According to that invention the carboxylic acid amide derivatives of formula (IA) can be prepared by the following processes:

a.) for producing of compounds of formula (IA) having -CO- group in place of X - wherein the meaning of R^1, R^2, Y, Z, U, V, W, n and m are as given before for the formula of (I) - a carboxylic acid of formula (II)



(II)

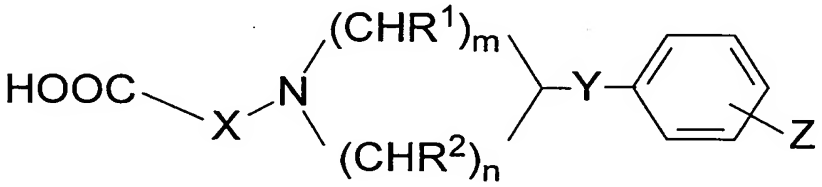
- wherein the meaning of U, V and W are as given for the formula of (IA) - or a reactive derivative of it is reacted with an amine of formula (III)



(III)

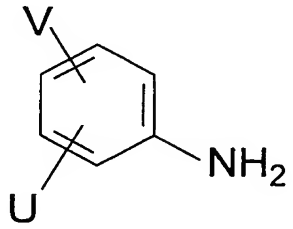
- wherein the meaning of R^1, R^2, Y, Z, n and m are as given before for the formula of (IA) - , or

b.) for producing of compounds of formula (IA) having -CO- group in place of W - wherein the meaning of R^1, R^2, Y, Z, U, V, X, n and m are as given before for the formula of (IA) - a carboxylic acid of formula (IV)



(IV)

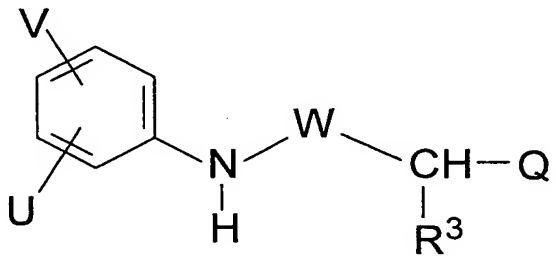
- wherein the meaning of X, R^1, R^2, Y, Z, n and m are as described above for the formula of (IA) - or a reactive derivative of it is reacted with an amine of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (IA) -, or

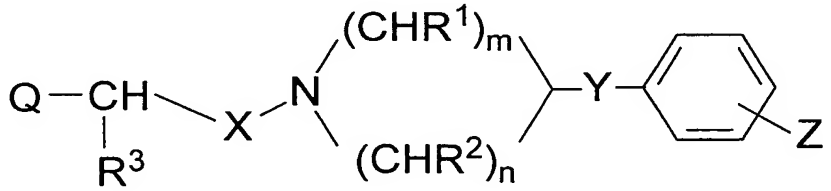
c.) for producing of compounds of formula (IA) having -CH_2- or -CH(-alkyl)- group in place of X - wherein alkyl is a C_1-C_4 alkyl group and the meaning of R^1, R^2, Y, Z, U, V, W, n and m are as given before for the formula of (IA) - a halogen derivative of a compound of formula (VI)



(VI)

- wherein the meaning of Q is halogen atom, R^3 is hydrogen atom or a C_1-C_4 alkyl group and U, V and W are as described above for the formula of (IA) - is reacted with an amine of formula (III) - wherein the meaning of R^1, R^2, Y, Z, n and m are as given before for the formula of (IA) -, or

d.) for producing of compounds of formula (IA) having -CH_2- or -CH(-alkyl)- group in place of W - wherein alkyl is a C_1-C_4 alkyl group and the meaning of R^1, R^2, Y, Z, U, V, X, n and m are as given before for the formula of (IA) - a halogen derivative of a compound of formula (VII)



(VII)

- wherein the meaning of Q is halogen atom, R^3 is hydrogen atom or a C_1-C_4 alkyl group and X, R^1, R^2, Y, Z, n and m are as described above for the formula of (IA) - is reacted with an amine of formula (V) - wherein the meaning of U and V are as given before for the formula of (IA) -,

and the obtained compounds of formula (IA) - where R^1, R^2, Y, Z, U, V, X, W, n and m are as defined above - in given case are transformed into an other compound of formula (IA) by

introducing further substituents and/or modifying and/or removing the existing ones, and/or formation of salts with acids and/or liberating the carboxylic acid amide derivative of formula (IA) from the obtained acid addition salts by treatment with a base and/or the free carboxylic acid amide derivative of formula (IA) can be transformed into a salt by treatment with a base and/or are resolved into their optical antipodes.

Exploration of the structure activity relationship requires large number of different analogues of the carboxylic acid amide of formula (IA) with diverse substituents. The previously reported procedures, however, utilizes the methodology of conventional organic synthesis that prevent their application in high throughput parallel synthesis.

Summary of the invention

We have now surprisingly found that it is possible to synthesize the required analogues of the carboxylic acid amide derivatives of formula (IA) using parallel synthesis as reported herein bellow, by using solid-supported scavenger reagents. The use of scavenger reagents allows the purification of the final product from excess reagents and catalysts by simple filtration. Procedures described in the present invention are suitable for automation and produce a large number of physically separated individual compounds over a short period of time. Moreover, it is possible to employ mild reaction conditions during the whole reaction sequence, obtaining high yields and purity degrees. Compounds obtained by this procedure are suitable for biological testing.

The invented new procedures give a large number of carboxylic acid amide derivatives of formula (I) in acceptable yield and in high purity enabled us to screen these compounds on biological test with high degree of confidence.

Detailed description of the invention

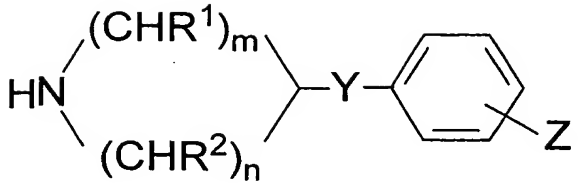
The present invention relates to two new processes for preparation of carboxylic acid amide derivatives of formula (I) - where R^1, R^2, Y, Z, U, V, X, n and m are as defined above - which are explained in the following as procedure "A" and "B".

Procedure "A"

for producing compound of formula (I), where X mean -CO- group and R^1, R^2, Y, Z, U, V, n and m are as defined for the formula (I).

Step 1:

secondary amines of formula (III)

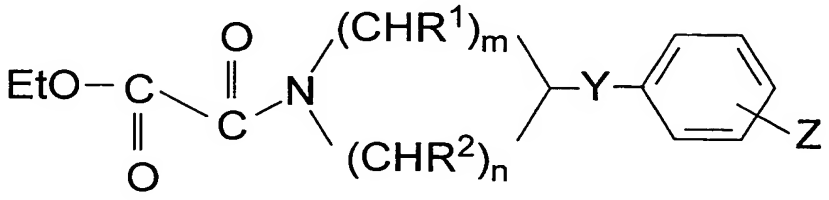


(III)

- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - are reacted with ethyl oxalylchloride in the presence of solid-supported base in dichloromethane.

Step 2:

the obtained ester compounds of formula (VIII)

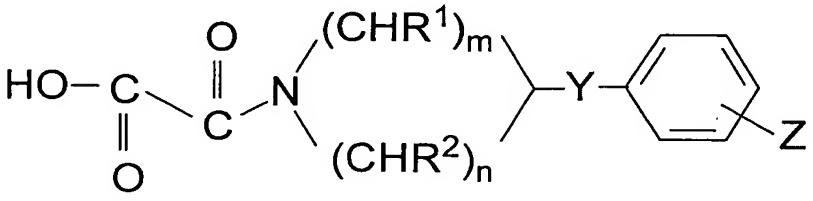


(VIII)

- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - are saponified with a strongly basic ion exchange resin in ethanol and

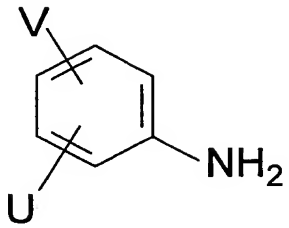
Step 3:

the obtained oxalic acid monoamides of formula (IX)



(IX)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) are reacted with amides of formula (V) -



(V)

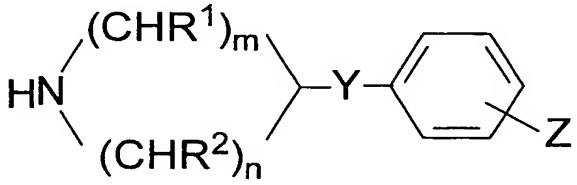
- wherein the meaning of U and V are as given before for the formula of (I) - in dichloromethan/dimethylformamide mixture in the presence of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide.

Procedure "B"

for producing compound of formula (I) - where X means $-CH_2-$ group and R^1, R^2, Y, Z, U, V, n and m are as defined above.

Step 1:

secondary amines of formula (III)

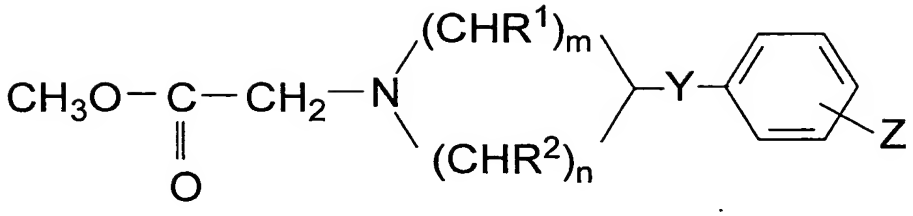


(III)

- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - are reacted with methyl bromoacetate in the presence of potassium carbonate in dimethylformamide,

Step 2:

the obtained ester compounds of formula (X)

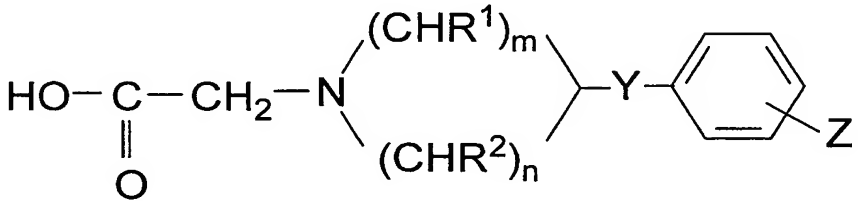


(X)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) are saponified with a strongly basic ion exchange resin in ethanol and

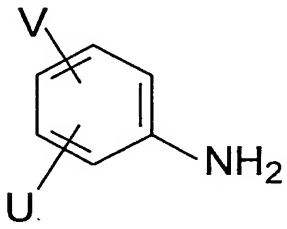
Step 3:

the obtained substituted glycines of formula (XI)



(XI)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) are reacted with amides of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (I) - in dichloromethan/dimethylformamide mixture in the presence of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide.

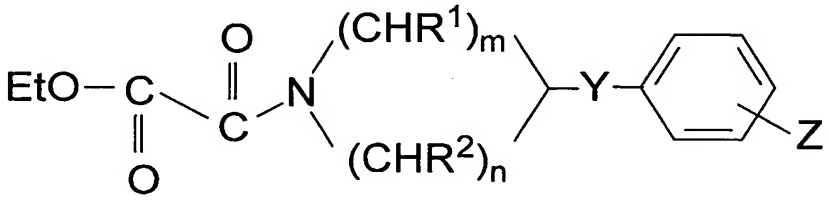
The following examples illustrate the invention without the intention of limitation anyway.

EXAMPLE 1

Procedure "A"

for producing compound of formula (I), where X mean -CO- group and R^1, R^2, Y, Z, U, V, n and m are as defined for the formula (I).

Step (1): Preparation of the ester compound of formula (VIII)

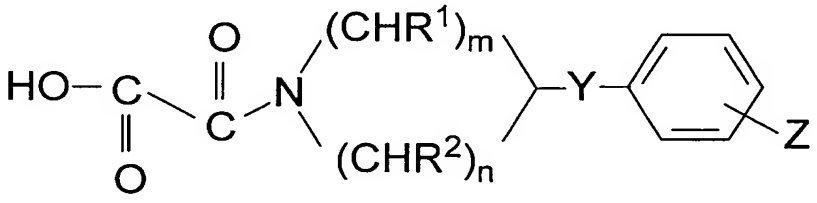


(VIII)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I).

0.1 mmol of a secondary amine of formula (III) - where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - is solved in 0.4 ml of CH_2Cl_2. Solid-supported base 2.5 (diisopropylaminomethylpolystyrene, 3 mmol/g, Fluka, cat.nr.: 38343) (83 mg) and 11.2 µl of ethyl oxalylchloride are added to the solution. The mixture is vigorously shaken for 2 hours at 40 °C. The slurry is filtered off, and the resin is washed 3 times with CH_2Cl_2. The filtrate is concentrated in vacuum. (yield: ~100 %)

Step (2): Hydrolysis of the above ester compound to oxalic acid monoamide of formula (IX)



(IX)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I).

The above obtained ester compound of formula (VIII) is solved in 0.8 ml of ethanol and 120 mg of strongly basic ion exchange resin (DOWEX-2X8-100) in OH^- form is added. The mixture is vigorously shaken for 16 hours at 60 °C, then the solvent is filtered off. The resin is

washed 3 times with ethanol. The resin then suspended in 0.8 ml of ethyl acetate, 0.8 ml of 1.5 M HCl / ethyl acetate is added and the mixture is vigorously shaken for 3 hours at room temperature. The resin is filtered off, washed with ethyl acetate and the filtrate is concentrated in vacuum. (yield: ~ 100 %)

Step (3): Coupling

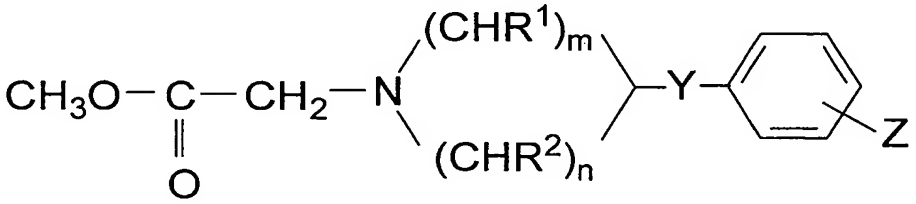
The above obtained oxalic acid monoamide of formula (IX) is solved in 2 ml of CH_2Cl_2 / DMF 1:1. 0.125 mmol of amine of formula (V) - where V and U mean as given for formula (I) - and 0.25 mmol of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide (EDC) are added and the mixture is vigorously shaken for 12 hours. The mixture is diluted with 2 ml of CH_2Cl_2, and extracted with 4 ml of water three times. Solid supported 4-benzyloxybenzaldehyde (200 mg, 3 mmol/g, Novabiochem, Cat.nr.: 01-64-0182) is added to the organic solution and the mixture is vigorously shaken for 2 hours at 40 °C. The resin is filtered off and the filtrate is concentrated to yield as final product the compound of formula (I) - where X mean -CO- group and R^1, R^2, Y, Z, U, V, n and m are as defined above.

EXAMPLE 2

Procedure "B"

for producing compound of formula (I) - where X means $-CH_2-$ group and R^1, R^2, Y, Z, U, V, n and m are as defined above.

Step (1): Preparation of the ester compound of formula (X)

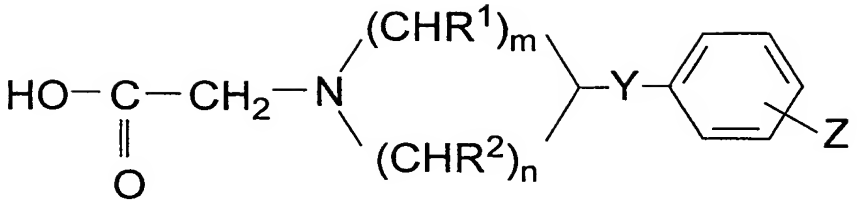


(X)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I).

0.1 mmol of a secondary amine of formula (III) - where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - and 0.04 g (0.28 mmol) of K_2CO_3 are solved in 0.8 ml of DMF. 12 µl (0.128 mmol) of methyl bromoacetate is added and the mixture is vigorously shaken for 3 hours. 1.6 ml of diethyl ether is added to the mixture, and the precipitated salts are filtered off. The filtrate is concentrated in vacuum. (yield: ~100 %)

Step (2): Hydrolysis of the above ester compound to substituted glycine of formula (XI)



(XI)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I).

The above obtained ester compound of formula (X) is solved in 0.8 ml of ethanol and 120 mg of strongly basic ion exchange resin (DOWEX-2X8-100) in OH^- form is added. The mixture is vigorously shaken for 16 hours at 60 °C, then the solvent is filtered off. The resin is washed 3 times with ethanol. The resin then suspended in 0.8 ml of ethyl acetate, 0.8 ml of 1.5 M HCl / ethyl acetate is added and the mixture is vigorously shaken for 3 hours at room temperature. The resin is filtered off, washed with ethyl acetate, and the filtrate is concentrated in vacuum. (yield: ~ 100 %)

Step (3): Coupling

The above obtained substituted glycine of formula (XI) is solved in 2 ml of CH_2Cl_2 / DMF 1:1. 0.125 mmol of amine of formula (V) - where V and U mean as given for formula (I) - and 0.25 mmol of EDC are added and the mixture is vigorously shaken for 12 hours. The mixture is diluted with 2 ml of CH_2Cl_2, and extracted with 4 ml of water three times. Solid-supported 4-benzyloxybenzaldehyde (200 mg, 3 mmol/g) is added to the organic solution, and the mixture is vigorously shaken for 2 hours at 40 °C. The resin is filtered off and the filtrate is concentrated to yield as final product the compound of formula (I) - where X means $-CH_2-$ group and R^1, R^2, Y, Z, U, V, n and m are as defined above.

EXAMPLE 3

Characterization and Purification Methods

Compounds of the present invention were characterized by high performance liquid chromatography coupled to mass selective detector (LC/MS) using HP 1100 Binary Gradient chromatography system with Microplate Sampler (Agilent, Waldbronn), controlled by ChemStation software. HP diode array detector was used to acquire UV spectra at 225 and 240 nm. All experiments were performed using HP MSD (Agilent, Waldbronn) single quadruple spectrometer equipped with an electrospray ionisation source to determine the structure.

The synthesized products were dissolved in 1 ml DMSO (Aldrich, Germany). 100 µl of each solution was diluted with DMSO to 1000 µl volume. Analytical chromatographic experiments were performed on Discovery RP C-16 Amide, 5 cm X 4.6 mm X 5 µm column from Supelco (Bellefonte, Pennsylvania) with a flow rate of 1 ml/minute for qualification. The obtained compounds were characterized by their k' value (purity, capacity factor). k' factors are evaluated by the following formula:

$$k' = (t_R - t_0) / t_0$$

where k'= capacity factor, t_R = retention time and t_0 = eluent retention time.

The A eluent was water containing 0.1% trifluoroacetic acid (TFA) (Sigma, Germany), the B eluent was 95% acetonitrile (Merck, Germany) containing 0.1% TFA and 5% A eluent. Gradient elution was used, starting with 100% A eluent and processing to 100% B eluent over a period of 5 minutes.

Semipreparative separation of the compounds of the present invention – purity below 85% - was carried out using the same high performance chromatography system. The separation was performed on Discovery RP C-16 Amide, 20 cm X 10 mm X 5 µm semipreparative column from Supelco (Bellefonte, Pennsylvania) with a flow rate of 3 ml/minutes. The fraction collection was based on mass selective separation. Gradient elution was used, starting with 80% A eluent and processing to 65% B eluent over a period of 35 minutes for those compounds where the capacity factor was more than 2.5. The gradient elution was changed, starting with 100 % A eluent and processing to 55% B eluent in 30 minutes for those compounds where the capacity factor was less than 2.5. The collected fractions were qualified by the above detailed analytical method and the solvent was evaporated by Speed Vac (Savant, USA).

The compounds prepared as described above in procedures "A" and "B" are shown in Table I, II, III and IV, respectively.

Table I

Compounds of formula (I) prepared by procedure "A" described in Example 1 where X means -CO- group, both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups, Y, Z, U and V are as given below:

No.	V	U	Y	Z	MW_c	MW_f	k'
1.	4- Ac-NH-	H-	$-CH_2-$	4-F-	397.45	398.5	3.421

2.	4- Ac-NH-	H-	$-CH_2-$	4-Cl-	413.905	414.5	3.202
3.	4- CH_3-SO_2-NH-	H-	-O-	4-CH_3-	431.507	432.5	3.349
4.	4- Ac-NH-	H-	-O-	4-CH_3-	395.459	396.4	3.306
5.	4- CH_3-SO_2-NH-	H-	-O-	4-Cl-	451.925	452.5	3.545
6.	4- CH_3-SO_2-NH-	H-	$-CH_2-$	4-Cl-	449.953	450.4	3.67
7.	4- Ac-NH-	H-	-O-	4-Cl-	415.877	416.5	3.518
8.	4- CH_3-SO_2-NH-	H-	$CH_3-N<$	4-Cl-	464.968	465.5	2.304
9.	4- Ac-NH-	H-	$CH_3-N<$	4-Cl-	428.92	429.5	2.259
10.	4- CH_3-SO_2-NH-	H-	$-CH_2-CH_2-$	4-F-	447.525	448.5	3.57
11.	4- Ac-NH-	H-	$-CH_2-CH_2-$	4-F-	411.477	412.5	3.555
12.	4- CH_3-SO_2-NH-	H-	$CH_3-N<$	4-CH_3-	444.55	445.5	1.155
13.	4- CH_3-SO_2-NH-	H-	$-CH_2-N(CH_3)-$	H-	444.55	445.4	1.776
14.	4- Ac-NH-	H-	$CH_3-N<$	4-Br-	473.371	474.4	2.33
15.	4- Ac-NH-	H-	$CH_3-N<$	4-CH_3-	408.502	409.5	2.169

Table II

Compounds of formula (I) prepared by procedure "A" described in Example 1 where X means -CO- group, both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups, U and V form together a bivalente group and Y and Z are as given below:

No.	V + U	Y	Z	MW_c	MW_f	k'
1.	3-4 -N=N-NH-	$-CH_2-$	4-F-	381.411	382.1	3.387
2.	3-4 -NH-CO-NH-	$-CH_2-$	4-CH_3-	392.459	393.1	3.386
3.	3-4 -O-CH_2-CO-NH-	$-CH_2-$	4-Cl-	427.888	428.5	3.691
4.	3-4 -N=N-NH-	$-CH_2-$	4-Cl-	397.866	398.5	3.592
5.	3-4 -CH_2-CH_2-CO-NH-	$-CH_2-$	4-Cl-	425.916	426.6	3.679
6.	3-4 -CH=N-NH-	-O-	4-CH_3-	378.432	379.5	3.385
7.	3-4 -CH=CH-NH-	-O-	4-CH_3-	377.444	378.5	3.55
8.	3-4 -CH_2-CH_2-CO-NH-	-O-	4-CH_3-	407.47	408.5	3.366
9.	3-4 -CH=CH-NH-	$-CH_2-$	4-F-	379.435	380.1	3.645
10.	3-4 -NH-CO-O-	$-CH_2-$	4-CH_3-	393.443	394.5	3.588
11.	3-4 -CH=N-NH-	$-CH_2-$	4-CH_3-	376.46	377.5	3.631

12.	3-4 -CH=CH-NH-	$-CH_2-$	4-CH_3-	375.472	376.5	3.78
13.	3-4 -N=N-NH-	$-CH_2-$	4-CH_3-	377.448	378.5	3.533
14.	3-4 $-CH_2-CH_2-$CO-NH-	$-CH_2-$	4-CH_3-	405.498	406.5	3.612
15.	3-4 -NH-CO-O-	-O-	4-Cl-	415.833	416.4	3.48
16.	3-4 $-O-CH_2-$CO-NH-	-O-	4-Cl-	429.86	430.5	3.516
17.	3-4 $-CH_2-CH_2-$CO-NH-	$-CH_2-$	4-F-	409.461	410.6	3.47
18.	3-4 -CH=N-NH-	$-CH_2-$	4-Cl-	396.878	397.4	3.697
19.	3-4 -CH=CH-NH-	$-CH_2-$	4-Cl-	395.89	396.5	3.839
20.	3-4 -CH=N-NH-	-O-	4-Cl-	398.85	399.5	3.523
21.	3-4 -CH=CH-NH-	-O-	4-Cl-	397.862	398.3	3.679
22.	3-4 -N=N-NH-	-O-	4-Cl-	399.838	400.6	3.422
23.	3-4 $-CH_2-CH_2-$CO-NH-	-O-	4-Cl-	427.888	428.5	3.504
24.	3-4 -N=N-NH-	-O-	4-CH_3-	379.42	380.1	3.281
25.	3-4 -NH-CO-O-	$CH_3-N<$	4-Cl-	428.876	429.5	2.37
26.	3-4 -NH-CO-NH-	$CH_3-N<$	4-Cl-	427.892	428.6	2.179
27.	3-4 -N=CH-NH-	$CH_3-N<$	4-Cl-	411.893	412.5	1.811
28.	3-4 $-O-CH_2-$CO-NH-	$CH_3-N<$	4-Cl-	442.903	443.5	2.39
29.	3-4 -CH=N-NH-	$CH_3-N<$	4-Cl-	411.893	412.5	2.359
30.	3-4 -N=N-NH-	$CH_3-N<$	4-Cl-	412.881	413.5	2.295
31.	3-4 $-CH_2-CH_2-$CO-NH-	$CH_3-N<$	4-Cl-	440.931	441.5	2.382
32.	3-4 -NH-CO-CO-NH-	$CH_3-N<$	4-Cl-	455.902	456.5	2.161
33.	3-4 -S-CO-NH-	$-CH_2-$	4-CH_3-	409.52	410.5	3.693
34.	3-4 -S-CO-NH-	$-CH_2-$	4-Cl-	429.93	430.4	3.751
35.	3-4 -NH-CS-NH-	-O-	4-CH_3-	410.5	411.5	3.155
36.	3-4 -S-CO-NH-	-O-	4-CH_3-	411.49	412.5	3.462
37.	3-4 -NH-CS-NH-	$CH_3-N<$	4-Cl-	443.96	444.5	2.250
38.	3-4 -S-CO-NH-	$CH_3-N<$	4-Cl-	444.95	445.5	2.55
39.	3-4 -NH-CO-O-	$-CH_2-CH_2-$	4-F-	411.433	412.5	3.56
40.	3-4 -N=CH-NH-	$-CH_2-CH_2-$	4-F-	394.45	395.5	3.028
41.	3-4 $-O-CH_2-$CO-NH-	$-CH_2-CH_2-$	4-F-	425.46	426.5	3.629
42.	3-4 -CH=N-NH-	$-CH_2-CH_2-$	4-F-	394.45	395.5	3.609

43.	3-4 -N=N-NH-	$-CH_2-CH_2-$	4-F-	395.438	396.5	3.517
44.	3-4 $-CH_2-CH_2-CO-NH-$	$-CH_2-CH_2-$	4-F-	423.488	424.5	3.591
45.	3-4 -NH-CS-NH-	$-CH_2-CH_2-$	4-F-	426.52	427.5	3.448
46.	3-4 -S-CO-NH-	$-CH_2-CH_2-$	4-F-	427.51	428.5	3.721
47.	3-4 -NH-CO-O-	$CH_3-N<$	$4-CH_3-$	408.458	409.5	2.244
48.	3-4 -N=CH-NH-	$CH_3-N<$	$4-CH_3-$	391.475	392.5	1.711
49.	3-4 $-O-CH_2-CO-NH-$	$CH_3-N<$	$4-CH_3-$	422.485	423.5	2.264
50.	3-4 -CH=N-NH-	$CH_3-N<$	$4-CH_3-$	391.475	392.5	2.237
51.	3-4 -N=N-NH-	$CH_3-N<$	$4-CH_3-$	392.463	393.5	2.165
52.	3-4 $-NH-C(CH_3)=N-$	$CH_3-N<$	$4-CH_3-$	405.502	406.5	1.813
53.	3-4 $-CH_2-CH_2-CO-NH-$	$CH_3-N<$	$4-CH_3-$	420.513	421.6	2.265
54.	3-4 -NH-CS-NH-	$CH_3-N<$	$4-CH_3-$	423.55	424.5	2.149
55.	3-4 -S-CO-NH-	$CH_3-N<$	$4-CH_3-$	424.53	425.5	2.439
56.	3-4 -NH-CS-NH-	$-CH_2-$	4-F-	412.5	413.5	3.376
57.	3-4 -S-CO-NH-	$-CH_2-$	4-F-	413.5	414.5	3.562
58.	3-4 -NH-CS-NH-	$-CH_2-$	4-Cl-	428.95	429.4	3.477
59.	3-4 -S-CO-NH-	-O-	4-Cl-	431.91	432.4	3.582
60.	3-4 -CH=CH-NH-	$-CH_2-CH_2-$	4-F-	393.462	394.5	3.74
61.	3-4 -CH=CH-NH-	$CH_3-N<$	4-Cl-	410.905	411.5	2.502
62.	3-4 -NH-CO-O-	$-CH_2-N(CH_3)-$	H-	408.458	409.4	1.882
63.	3-4 $-O-CH_2-CO-NH-$	$-CH_2-N(CH_3)-$	H-	422.485	423.5	1.925
64.	3-4 -CH=CH-NH-	$-CH_2-N(CH_3)-$	H-	390.487	391.4	1.945
65.	3-4 -NH-CS-NH-	$-CH_2-N(CH_3)-$	H-	423.535	424.5	1.834
66.	3-4 -S-CO-NH-	$-CH_2-N(CH_3)-$	H-	424.519	425.5	2.108
67.	3-4 -NH-CO-O-	$CH_3-N<$	4-Br-	473.327	474.3	2.404
68.	3-4 -NH-CO-NH-	$CH_3-N<$	4-Br-	472.343	473.4	2.218
69.	3-4 -N=CH-NH-	$CH_3-N<$	4-Br-	456.344	457.4	1.839
70.	3-4 $-O-CH_2-CO-NH-$	$CH_3-N<$	4-Br-	487.354	488.4	2.428
71.	3-4 -CH=CH-NH-	$CH_3-N<$	4-Br-	455.356	456.4	2.539
72.	3-4 $-CH_2-CH_2-CO-NH-$	$CH_3-N<$	4-Br-	485.382	486.4	2.429

Table III

Compounds of formula (I) prepared by procedure "B" described in Example 2 where X means -CH_2- group, both of -$(CHR^1)_m$- and -$(CHR^2)_n$- are -CH_2-CH_2- groups Y, Z, U and V are as given below:

No.	V	U	Y	Z	MW_c	MW_f	k'
1.	4- Ac-NH-	H-	-CH_2-	H-	365.477	366.5	2.272
2.	4- CH_3-SO_2-NH-	H-	-CH_2-	4-F-	419.515	420.5	2.335
3.	4- Ac-NH-	H-	-CH_2-	4-F-	383.467	384.5	2.366
4.	4- HO-	H-	-CH_2-	4-F-	342.413	343.5	2.100
5.	4- Ac-NH-	H-	-CH_2-	4-Cl-	399.922	400.5	2.644
6.	4- CH_3-SO_2-NH-	H-	-CH_2-	4-Cl-	435.97	436.5	2.649
7.	4- HO-	H-	-CH_2-	4-Cl-	358.869	359.4	2.48
8.	4- CH_3-SO_2-NH-	H-	-O-	4-Cl-	437.942	438.4	2.455
9.	4- Ac-NH-	H-	-O-	4-Cl-	401.894	402.5	3.35
10.	4- HO-	H-	-O-	4-Cl-	360.841	361.4	2.264
11.	4- Ac-NH-	H-	-O-	4-CH_3-	381.476	382.5	2.329
12.	4- HO-	H-	-O-	4-CH_3-	340.423	341.4	2.112
13	4- CH_3-SO_2-NH-	H-	-CH_2-	4-CH_3-	415.552	416.6	2.539
14	4- Ac-NH-	H-	-CH_2-	4-CH_3-	379.504	380.5	2.527
15.	4- HO-	H-	-CH_2-	4-CH_3-	338.451	339.5	2.33
16.	4- HO-	H-	CH_3-N<	4-Cl-	373.884	374.4	1.369
17.	4- Ac-NH-	H-	CH_3-N<	4-Cl-	414.937	415.4	1.785
18.	4- CH_3-SO_2-NH-	H-	CH_3-N<	4-Cl-	450.985	451.5	1.704
19.	4- CH_3-SO_2-NH-	H-	-CH_2-CH_2-	4-F-	433.542	434.3	2.504
20.	4- Ac-NH-	H-	-CH_2-CH_2-	4-F-	397.494	398.2	2.53
21.	4- HO-	H-	-CH_2-CH_2-	4-F-	356.441	357.2	2.325
22.	4- CH_3-SO_2-NH-	H-	CH_3-N<	4-CH_3-	430.567	431.3	1.332
23.	4- Ac-NH-	H-	CH_3-N<	4-CH_3-	394.519	395.3	1.433
24.	4- Ac-NH-	H-	CH_3-N<	4-Br-	459.388	460.2	1.864
25.	4- HO-	H-	CH_3-N<	4-Br-	418.335	419.2	1.461
26.	4- CH_3-SO_2-NH-	H-	CH_3-N<	4-Br-	495.436	496.3	1.793

27.	4- HO-	H-	CH_3-N<	4-CH_3-	353.466	354.3	1.027

Table IV

Compounds of formula (I) prepared by procedure "B" described in Example 2 where X means -CH_2- group, both of -$(CHR^1)_m$- and -$(CHR^2)_n$- are -CH_2-CH_2- groups, U and V form together a bivalente group and Y and Z are as given below:

No.	V + U	Y	Z	MW_c	MW_f	k'
1.	3-4 -NH-CO-O-	-CH_2-	H-	365.433	366.4	2.297
2.	3-4 -N=CH-NH-	-CH_2-	H-	348.45	349.4	1.708
3.	3-4 -NH-N=CH-	-CH_2-	H-	348.45	349.4	2.392
4.	3-4 -CH=N-NH-	-CH_2-	H-	348.45	349.4	2.36
5.	3-4 -CH=CH-NH-	-CH_2-	H-	347.462	348.4	2.449
6.	3-4 -N=N-NH-	-CH_2-	H-	349.438	350.4	2.286
7.	3-4 -S-C(SH)=N-	-CH_2-	H-	397.555	398.4	2.729
8.	3-4 -CH=C(CH_3)-NH-	-CH_2-	H-	361.489	362.5	2.656
9.	3-4 -NH-C(CH_3)=N-	-CH_2-	H-	362.477	363.5	1.849
10.	3-4 -CH_2-CH_2-CO-NH-	-CH_2-	H-	377.488	378.5	2.376
11.	3-4 -S-CO-NH-	-CH_2-	H-	381.494	382.5	2.516
12.	3-4 -NH-CO-O-	-CH_2-	4-F-	383.423	384.4	2.408
13.	3-4 -N=CH-NH-	-CH_2-	4-F-	366.44	367.5	1.808
14.	3-4 -O-CH_2-CO-NH-	-CH_2-	4-F-	397.45	398.5	2.445
15.	3-4 -NH-N=CH-	-CH_2-	4-F-	366.44	367.5	2.483
16.	3-4 -CH=N-NH-	-CH_2-	4-F-	366.44	367.5	2.446
17.	3-4 -CH=CH-NH-	-CH_2-	4-F-	365.452	366.5	2.558
18.	3-4 -N=N-NH-	-CH_2-	4-F-	367.428	368.5	2.381
19.	3-4 -S-C(SH)=N-	-CH_2-	4-F-	415.545	416.5	2.788
20.	3-4 -CH=C(CH_3)-NH-	-CH_2-	4-F-	379.479	380.5	2.743
21.	3-4 -NH-C(CH_3)=N-	-CH_2-	4-F-	380.467	381.5	1.942
22.	3-4 -CH_2-CH_2-CO-NH-	-CH_2-	4-F-	395.478	396.5	2.455
23.	3-4 -NH-CS-NH-	-CH_2-	4-F-	398.5	399.5	2.349
24.	3-4 -S-CO-NH-	-CH_2-	4-F-	399.484	400.4	1.59

25.	3-4 -N=CH-NH-	$-CH_2-$	$4-CH_3-$	362.477	363.5	2.002
26.	3-4 -O-CO-NH-	$-CH_2-$	4-Cl-	399.878	400.4	2.687
27.	3-4 -NH-CO-O-	$-CH_2-$	4-Cl-	399.878	400.4	2.669
28.	3-4 -CH=CH-NH-	$-CH_2-$	4-Cl-	381.907	382.5	2.827
29.	3-4 -S-C(SH)=N-	$-CH_2-$	4-Cl-	432.00	432.4	3.006
30.	3-4 $-CH=C(CH_3)-NH-$	$-CH_2-$	4-Cl-	395.934	396.5	2.972
31.	3-4 $-NH-C(CH_3)=N-$	$-CH_2-$	4-Cl-	396.922	397.5	2.222
32.	3-4 $-CH_2-CH_2-CO-NH-$	$-CH_2-$	4-Cl-	411.933	412.5	2.727
33.	3-4 $-CH_2-CO-NH-$	$-CH_2-$	4-Cl-	397.906	398.5	2.616
34.	3-4 -N=CH-NH-	$-CH_2-$	4-Cl-	382.895	383.5	2.154
35.	3-4 $-O-CH_2-CO-NH-$	$-CH_2-$	4-Cl-	413.905	414.5	2.724
36.	3-4 -NH-CS-NH-	$-CH_2-$	4-Cl-	414.955	415.4	2.616
37.	3-4 -S-CO-NH-	$-CH_2-$	4-Cl-	415.939	416.4	2.105
38.	3-4 -O-CO-NH-	-O-	4-Cl-	401.85	402.4	2.513
39.	3-4 -NH-CO-O-	-O-	4-Cl-	401.85	402.4	2.481
40.	3-4 -N=CH-NH-	-O-	4-Cl-	384.867	385.5	1.93
41.	3-4 $-O-CH_2-CO-NH-$	-O-	4-Cl-	415.877	416.4	2.54
42.	3-4 -NH-N=CH-	-O-	4-Cl-	384.867	385.4	2.575
43.	3-4 -CH=N-NH-	-O-	4-Cl-	384.867	385.4	2.544
44.	3-4 -CH=CH-NH-	-O-	4-Cl-	383.879	384.4	2.646
45.	3-4 $-CH=C(CH_3)-NH-$	-O-	4-Cl-	397.906	398.5	2.807
46.	3-4 $-NH-C(CH_3)=N-$	-O-	4-Cl-	398.894	399.4	2.058
47.	3-4 $-CH_2-CH_2-CO-NH-$	-O-	4-Cl-	413.905	414.5	2.56
48.	3-4 -S-CO-NH-	-O-	4-Cl-	417.911	418.4	2.677
49.	3-4 -O-CO-NH-	-O-	$4-CH_3-$	381.432	382.4	2.391
50.	3-4 -NH-CO-O-	-O-	$4-CH_3-$	381.432	382.5	2.374
51.	3-4 -NH-CO-NH-	-O-	$4-CH_3-$	380.448	381.5	2.255
52.	3-4 $-CH_2-CO-NH-$	-O-	$4-CH_3-$	379.46	380.5	2.296
53.	3-4 -N=CH-NH-	-O-	$4-CH_3-$	364.449	365.5	1.841
54.	3-4 $-O-CH_2-CO-NH-$	-O-	$4-CH_3-$	395.459	396.5	2.419
55.	3-4 -NH-N=CH-	-O-	$4-CH_3-$	364.449	365.5	2.466

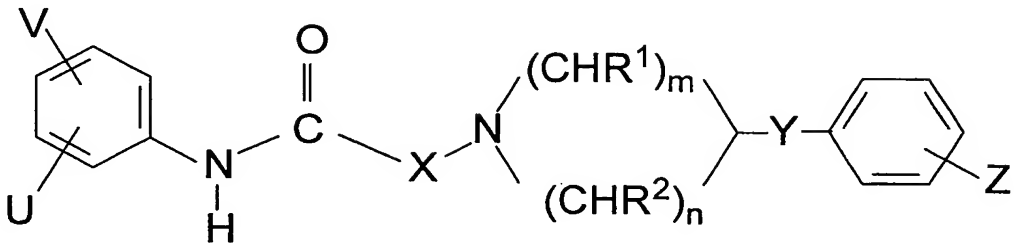
56.	3-4 -CH=N-NH-	-O-	4-CH_3-	364.449	365.5	2.418
57.	3-4 -S-C(SH)=N-	-O-	4-CH_3-	413.554	414.4	2.74
58.	3-4 -CH=C(CH_3)-NH-	-O-	4-CH_3-	377.488	378.5	2.702
59.	3-4 -NH-C(CH_3)=N-	-O-	4-CH_3-	378.476	380.5	1.946
60.	3-4 -CH_2-CH_2-CO-NH-	-O-	4-CH_3-	393.487	394.5	2.438
61.	3-4 -NH-CS-NH-	-O-	4-CH_3-	396.509	397.5	2.327
62.	3-4 -O-CO-NH-	-CH_2-	4-CH_3-	379.46	380.5	2.574
63.	3-4 -NH-CO-O-	-CH_2-	4-CH_3-	379.46	380.5	2.544
64.	3-4 -NH-CO-NH-	-CH_2-	4-CH_3-	378.476	379.5	2.433
65.	3-4 -CH_2-CO-NH-	-CH_2-	4-CH_3-	377.488	378.5	2.486
66.	3-4 -O-CH_2-CO-NH-	-CH_2-	4-CH_3-	393.487	394.5	2.592
67.	3-4 -NH-N=CH-	-CH_2-	4-CH_3-	362.477	363.5	2.645
68.	3-4 -CH=N-NH-	-CH_2-	4-CH_3-	362.477	363.5	2.618
69.	3-4 -CH=CH-NH-	-CH_2-	4-CH_3-	361.489	362.5	2.735
70.	3-4 -S-C(SH)=N-	-CH_2-	4-CH_3-	411.582	412.5	2.919
71.	3-4 -CH=C(CH_3)-NH-	-CH_2-	4-CH_3-	375.516	376.5	2.885
72.	3-4 -NH-C(CH_3)=N-	-CH_2-	4-CH_3-	376.504	377.4	2.100
73.	3-4 -CH_2-CH_2-CO-NH-	-CH_2-	4-CH_3-	391.515	392.5	2.612
74.	3-4 -NH-CS-NH-	-CH_2-	4-CH_3-	394.537	395.5	2.500
75.	3-4 -S-CO-NH-	-CH_2-	4-CH_3-	395.521	396.5	2.733
76.	3-4 -N=CH-NH-	CH_3-N<	4-Cl-	397.91	398.5	1.296
77.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-Cl-	428.92	429.5	1.896
78.	3-4 -S-C(SH)=N-	CH_3-N<	4-Cl-	447.015	447.5	2.285
79.	3-4 -NH-C(CH_3)=N-	CH_3-N<	4-Cl-	411.937	412.4	1.455
80.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-Cl-	426.948	427.4	1.937
81.	3-4 -CH_2-CO-NH-	-O-	4-Cl-	399.878	400.4	2.43
82.	3-4 -O-CO-NH-	CH_3-N<	4-Cl-	414.893	415.5	1.827
83.	3-4 -CH=N-NH-	CH_3-N<	4-Cl-	397.91	398.5	1.853
84.	3-4 -NH-N=CH-	CH_3-N<	4-Cl-	397.91	398.5	1.932
85.	3-4 -CH=CH-NH-	CH_3-N<	4-Cl-	396.922	397.5	1.862
86.	3-4 -CH=C(CH_3)-NH-	CH_3-N<	4-Cl-	410.949	411.4	2.130

87.	3-4 -S-CO-NH-	CH_3-N<	4-Cl-	430.954	431.4	2.072
88.	3-4 -O-CO-NH-	-CH_2-CH_2-	4-F-	397.45	398.3	2.558
89.	3-4 -NH-CO-O-	-CH_2-CH_2-	4-F-	397.45	398.3	2.525
90.	3-4 -CH_2-CO-NH-	-CH_2-CH_2-	4-F-	395.478	396.2	2.481
91.	3-4 -N=CH-NH-	-CH_2-CH_2-	4-F-	380.467	381.2	1.988
92.	3-4 -O-CH_2-CO-NH-	-CH_2-CH_2-	4-F-	411.477	412.2	2.585
93.	3-4 -NH-N=CH-	-CH_2-CH_2-	4-F-	380.467	381.2	2.623
94.	3-4 -CH=N-NH-	-CH_2-CH_2-	4-F-	380.467	381.2	2.601
95.	3-4 -CH=CH-NH-	-CH_2-CH_2-	4-F-	379.479	380.2	2.696
96.	3-4 -S-C(SH)=N-	-CH_2-CH_2-	4-F-	429.572	430.4	2.881
97.	3-4 -CH=C(CH_3)-NH-	-CH_2-CH_2-	4-F-	393.506	394.2	2.851
98.	3-4 -NH-C(CH_3)=N-	-CH_2-CH_2-	4-F-	394.494	395.2	2.085
99.	3-4 -CH_2-CH_2-CO-NH-	-CH_2-CH_2-	4-F-	409.505	410.2	2.602
100.	3-4 -NH-CS-NH-	-CH_2-CH_2-	4-F-	412.527	413.2	2.475
101.	3-4 -S-CO-NH-	-CH_2-CH_2-	4-F-	413.511	414.3	2.716
102.	3-4 -O-CO-NH-	CH_3-N<	4-CH_3-	394.475	395.2	1.467
103.	3-4 -NH-CO-O-	CH_3-N<	4-CH_3-	394.475	395.2	1.48
104	3-4 -NH-CO-NH-	CH_3-N<	4-CH_3-	393.491	394.2	1.423
105.	3-4 -CH_2-CO-NH-	CH_3-N<	4-CH_3-	392.503	393.3	1.444
106.	3-4 -N=CH-NH-	CH_3-N<	4-CH_3-	377.492	378.2	0.966
107.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-CH_3-	408.502	409.3	1.544
108.	3-4 -CH=CH-NH-	CH_3-N<	4-CH_3-	376.504	377.2	1.453
109.	3-4 -S-C(SH)=N-	CH_3-N<	4-CH_3-	426.597	427.3	1.896
110.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-CH_3-	406.53	407.3	1.574
111.	3-4 -NH-CS-NH-	CH_3-N<	4-CH_3-	409.552	410.3	1.455
112.	3-4 -S-CO-NH-	CH_3-N<	4-CH_3-	410.536	410.3	1.682
113.	3-4 -CH=C(CH_3)-NH-	CH_3-N<	4-Br-	455.4	456.2	2.211
114.	3-4 -NH-C(CH_3)=N-	CH_3-N<	4-Br-	456.388	457.2	1.522
115.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-Br-	471.399	472.8	2.001
116.	3-4 -S-CO-NH-	CH_3-N<	4-Br-	475.405	476.2	2.159
117.	3-4 -CH=C(CH_3)-NH-	CH_3-N<	4-CH_3-	390.531	391.3	1.708

118.	3-4 -CH=N-NH-	CH_3-N<	4-CH_3-	377.492	378.3	1.495
119.	3-4 -NH-N=CH-	CH_3-N<	4-CH_3-	377.492	378.3	1.572
120.	3-4 -O-CO-NH-	CH_3-N<	4-Br-	459.344	460.2	1.913
121.	3-4 -CH_2-CO-NH-	CH_3-N<	4-Br-	457.372	458.2	1.839
122.	3-4 -N=CH-NH-	CH_3-N<	4-Br-	442.361	443.2	1.39
123.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-Br-	473.371	474.2	1.986
124.	3-4 -NH-N=CH-	CH_3-N<	4-Br-	442.361	443.2	2.023
125.	3-4 -CH=N-NH-	CH_3-N<	4-Br-	442.361	443.2	1.949
126.	3-4 -CH=CH-NH-	CH_3-N<	4-Br-	441.373	442.2	1.953
127.	3-4 -S-C(SH)=N-	CH_3-N<	4-Br-	491.466	492.2	2.371
128.	3-4 -NH-CS-NH-	CH_3-N<	4-Br-	474.421	475.2	1.897
129.	3-4 -NH-C(CH_3)=N-	CH_3-N<	4-CH_3-	391.519	392.3	1.151
130.	3-4 -NH-CO-O-	CH_3-N<	4-Br-	459.344	460.2	1.908

What we claim is:

1. New solid-supported parallel synthesis process for preparation of carboxylic acid amide derivatives of formula (I)



(I)

- wherein

V and U independently are hydrogen or halogen atom, hydroxyl, cyano, nitro, amino, C_1-C_4 alkylamino optionally substituted by a halogen atom or halogen atoms , arylamino optionally substituted by a halogen atom or halogen atoms , aralkylamino optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkylsulfonamido optionally substituted by a halogen atom or halogen atoms, C_1-C_4 alkanoylamido optionally substituted by a halogen atom or halogen atoms, arylsulfonamido, C_1-C_4 alkylsulfonyloxy, carboxyl, trifluoromethyl, trifluoromethoxy, C_1-C_4 alkyl-SO_2-NH-CH_2-, NH_2-$(CH_2)_{1-4}$-SO_2-NH-, NH_2-$(CH_2)_{1-4}$-(CO)-NH-, sulfamoyl [NH_2-SO_2-], formyl [-CHO], amino-methyl [-CH_2-NH_2], hydroxymethyl, C_1-C_4 alkyl, C_1-C_4 alkoxymethyl, halogenomethyl, tetrazolyl group, or C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkanoyloxy, phenyl or C_1-C_4 alkoxy groups, optionally substituted by amino group, or

the neighbouring V and U groups in given case together with one or more identical or different additional hetero atom and -CH= and/or -CH_2- groups can form an optionally substituted 4-7 membered homo- or heterocyclic ring, preferably morpholine, pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

X stands for -CO- or -CH_2- group,

Y is oxygen atom, as well as C_1-C_4 alkylene, C_1-C_4 alkynylene, cycloalkylene, aminocarbonyl, -NH-, -N(alkyl)-, $-CH_2O-$, -CH(OH)-, $-OCH_2-$ group, - wherein alkyl is a C_1-C_4 alkyl group -,

Z is hydrogen or halogen atom, nitro, amino, C_1-C_4 alkyl, C_1-C_4 alkoxy, cyano, trifluoromethyl, hydroxyl or carboxyl group,

R^1 and R^2 independently are hydrogen atom or alkyl group, or R^1 and R^2 together form an optionally substituted C_1-C_3 bridge and

n and m independently are 0-3, with the restriction, that n and m can not be 0 at the same time,

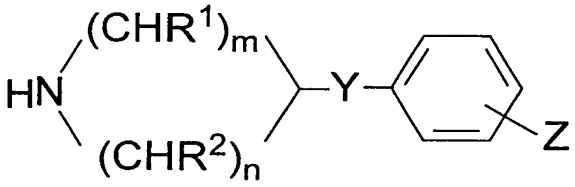
and optical antipodes or racemates and/or pharmaceutically acceptable salts thereof formed with acids and bases with the proviso that

when Z means hydrogen atom, Y means $-CH_2-$ group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, X means $-CH_2-$ group and V means hydrogen atom, then the meaning of U is other than a 4-bromo substituent and

when Z means hydrogen atom, Y means $-CH_2-$ group, both of m and n mean 2, both of R^1 and R^2 mean hydrogen atom, X mean -CO- group and V means hydrogen atom, then the meaning of U is other than a 4-carboxyl or 4-etoxycarbonyl substituent -

characterized that,

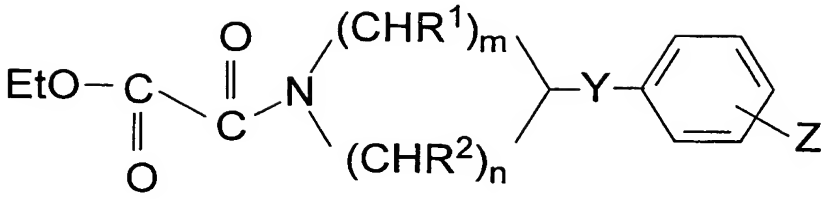
a.) for producing compound of formula (I), where X mean -CO- group and R^1, R^2, Y, Z, U, V, n and m are as defined for the formula (I), secondary amines of formula (III)



(III)

- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - are reacted with ethyl oxalylchloride in the presence of solid-supported base in dichloromethane,

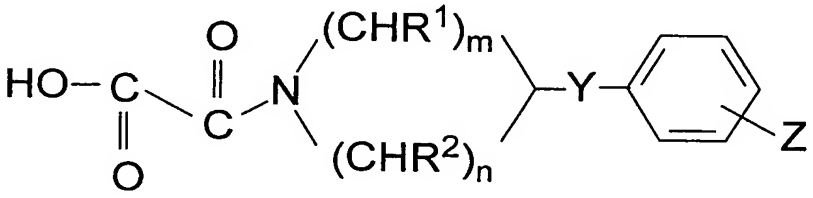
the obtained ester compounds of formula (VIII)



(VIII)

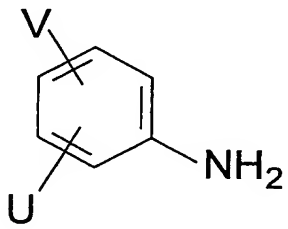
- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - are saponified with a strongly basic ion exchange resin in ethanol and

the obtained oxalamid acids of formula (IX)



(IX)

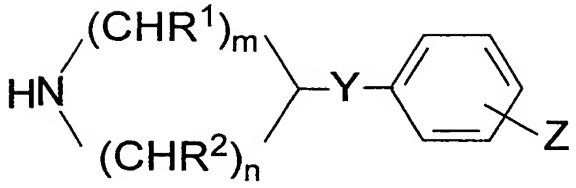
where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) are reacted with amides of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (I) - in dichloromethan/dimethylformamide mixture in the presence of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide, or

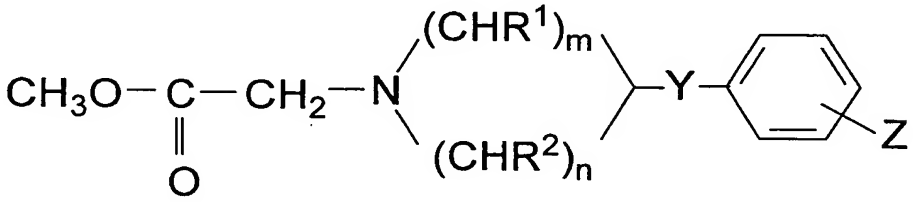
b.) for producing compound of formula (I), where X mean $-CH_2-$ group and R^1, R^2, Y, Z, U, V, n and m are as defined for the formula (I), secondary amines of formula (III)



(III)

- where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) - are reacted with methyl bromoacetate in the presence of potassium carbonate in dimethylformamide,

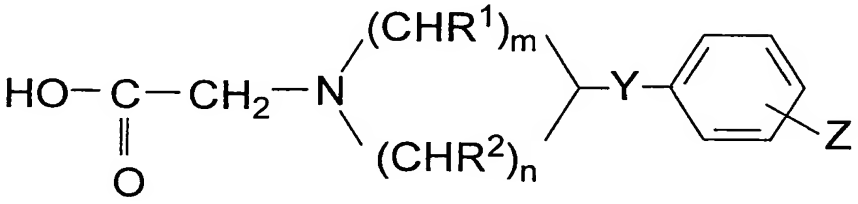
the obtained ester compounds of formula (X)



(X)

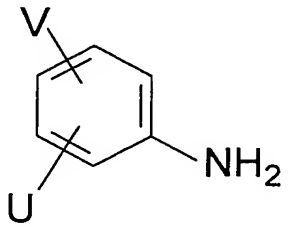
where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) are saponified with a strongly basic ion exchange resin in ethanol and

the obtained substituted glycines of formula (XI)



(XI)

where R^1, R^2, m, n, Y and Z have the same meaning as given for formula (I) are reacted with amides of formula (V)



(V)

- wherein the meaning of U and V are as given before for the formula of (I) - in dichloromethan/dimethylformamide mixture in presence of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide.

RICHTER GEDEON VEGYÉSZETI GYÁR R.T.